REMARKS/ARGUMENTS

Claims 28-32 are pending in this application. Applicants note and appreciate the withdrawal of the earlier objections and rejection under 35 U.S.C. §112, second paragraph.

The remaining rejections of Claims 28-32 under 35 U.S.C. §101, §112, first paragraph and §102(a), are addressed below.

Priority Determination

The Examiner maintains that the effective filing date for the application is December 6, 2001, the actual filing date of the instant application, and that Applicants are not entitled to claim priority to earlier-filed U.S. Provisional Patent Application Serial No. 60/162,506, filed October 29, 1999, "since said prior application does not provide a specific and substantial asserted utility or a well established utility for the claimed invention." See pages 2-3 of the instant Office Action.

As discussed previously in the Applicants' response filed on August 19, 2004, Applicants rely on the gene amplification assay (Example 143) for patentable utility which was first disclosed in U.S. Provisional Patent Application Serial No. 60/162,506, filed October 29, 1999, priority to which has been claimed in this application.

Applicants respectfully maintain the position that that the specification provides the support required to establish utility for the claimed antibodies, for example, in detecting over-expression or absence of expression of the PRO1293 polypeptide for the reasons previously set forth in the Applicants' response filed on August 19, 2004. Accordingly, Applicants submit that the subject matter of the instant claims is supported by the disclosure in U.S. Provisional Patent Application Serial No. 60/162,506. Therefore, the effective filing date of this application is October 29, 1999, the filing date of U.S. Provisional Patent Application Serial No. 60/162,506.

Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph

Claims 28-32 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 28-32 further remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ..., one skilled in the art would not know how to use the claimed invention."

The Examiner specifically asserts that "Applicant's argument (submitted with the amendment of 19 August 2004) have been fully considered but not found to be persuasive." The Examiner further asserts that "[t]he Ashkenazi, Dr. Goddard and Polakis declarations under 37 C.F.R. §1.132 on 19 August 2004 are also insufficient to overcome the rejection of Claims 28-32, based upon 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph." (See page 4 of the instant Office Action).

Further, based on a reference by Hu *et al.*, the Examiner alleges that "the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue." In particular, the Examiner contends that Hu *et al.* "analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray." Furthermore, the Examiner asserts that Hu *et al.* discovered that:

> for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was strong and significant correlation between expression level and a published role in the disease.

Applicants respectfully disagree and traverse the rejection.

First of all, Applicants respectfully maintain the position that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1293 nucleic acids for

the reasons previously set forth in the Applicants' response filed on August 19, 2004.

Secondly, the Examiner's conclusions that Hu *et al.* shows that gene amplification does not *necessarily* result in increased expression at the mRNA and polypeptide levels is flawed for several reasons. As discussed in the Applicants' response filed on August 19, 2004, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such correlation is **more likely than not to exist**.

Further, contrary to the Examiner's assertion, Applicants respectfully submit that Hu *et al.* does not conclusively show that it is more likely than not the gene amplification does not result in increased expression at the mRNA and polypeptide levels.

First, the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based a statistical analysis of the information disclosed in published literatures. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships." In particular, Hu *et al.* relied on MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column).

Therefore, Applicants first submit that the reference by Hu *et al.* only studies the statistical analysis of micro-array data and not the gene amplification data. Hence, their findings would not be directly applicable to the gene amplification data. In addition, Applicants respectfully submit that the Hu *et al.* reference does not show a lack of correlation between microarray data and the biological significance of cancer genes is typical.

According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the

strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules were overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusion based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al.* admit that "[i]t is likely that this threshold will change depending on the disease as well

as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added).

In summary, Applicants respectfully submit that the Examiner has not shown that a lack of correlation between microarray data and the biological significance of cancer genes, as observed for ER-positive breast tumor, is typical. Accordingly, the Examiner has not shown that a lack of correlation between gene amplification data and the biological significance of cancer genes is typical.

Accordingly, Applicants respectfully submit that Applicants have shown that when the proper legal standard for utility is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the PRO1293 polypeptide and its antibodies. Hence, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1293 polypeptide and its antibodies, for example, in detecting over-expression or absence of expression of PRO1293. Based on these discussions and for the reasons previously set forth in the Applicants' response filed on August 19, 2004, one skilled in the art, at the time the application was filed, would know how to use the claimed antibodies in a method for the diagnosis of lung or colon cancer.

In view of the above, Applicants request the Examiner to reconsider and withdraw the rejection of Claims 28-32 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 U.S.C. §102

The examiner contends that the priority of the instant application is set at December 6, 2001. As discussed above, Applicants respectfully submit that the effective filing date of the present application is October 29, 1999.

Claims 28-33 stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Bostein *et al.*, WO 2000053751, published on September 14, 2000.

As discussed above , Applicants are entitled to an effective filing date of October 29, 1999, and hence, Bostein *et al.* is not prior art under 102(a) since its filing date is after the effective priority date of this application. Therefore, Applicants respectfully maintain the position that that Claims 28-32 are not anticipated by Botstein *et al.* for the reasons previously set forth in the Applicants' response filed on August 19, 2004.

Accordingly, Applicants respectfully request that this rejection to Claims 28-32 be withdrawn.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C4**).

Respectfully submitted,

Date: February 28, 2005

By: _____
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